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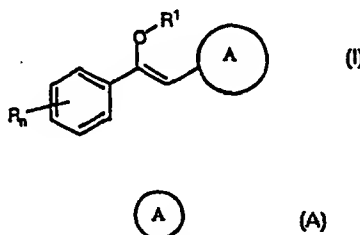
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<p>(21) International Application Number: PCT/EP98/04890 (22) International Filing Date: 6 August 1998 (06.08.98) (30) Priority Data: 97114065.2 14 August 1997 (14.08.97) EP (71) Applicant: F. HOFFMANN-LA ROCHE AG [CH/CH]; 124 Grenzacherstrasse, CH-4070 Basle (CH). (72) Inventors: ADAM, Geo; Untere Staltenstrasse 8, D-79650 Schopfheim (DE). KOLCZEWSKI, Sabine; Binzener Strasse 7a, D-79539 Lörrach (DE). MUTEL, Vincent; 15, place des Maréchaux, F-68100 Mulhouse (FR). STADLER, Heinz; Waldhofstrasse 37, CH-4310 Rheinfelden (CH). WICHMANN, Jürgen; Im Wolfischbühl 32, D-79585 Steinen (DE). WOLTERING, Thomas, Johannes; Riedlistrasse 13, D-79576 Weil am Rhein (DE). (74) Agent: POPPE, Regina; Grenzacherstrasse 124, CH-4070 Basle (CH).</p>		<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</p>

(54) Title: HETEROCYCLIC VINYLETHERS AGAINST NEUROLOGICAL DISORDERS



(57) Abstract

The invention is concerned with the use of compounds of general formula (I), wherein R signifies halogen or lower alkyl; n signifies 0-3; R<sup>1</sup> signifies lower alkyl; cycloalkyl; benzyl optionally substituted by hydroxy, halogen, lower alkoxy or lower alkyl; benzoyl optionally substituted by amino, lower alkylamino or di-lower alkylamino; acetyl or cycloalkyl-carbonyl; and (A) signifies an aromatic 5-membered residue which is bonded via a N-atom and which contains further 1-3 N atoms in addition to the linking N atom, as well as their pharmaceutically acceptable salts as therapeutically active substances, especially for the control or prevention of acute and/or chronic neurological disorders.

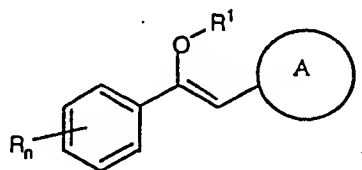
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## Heterocyclic vinylethers against neurological disorders

The present invention is concerned with heterocyclic vinyl ethers of the general formula



wherein

R signifies halogen or lower alkyl;

n signifies 0-3;

10 R<sup>1</sup> signifies lower alkyl; cycloalkyl; benzyl optionally substituted by hydroxy, halogen, lower alkoxy or lower alkyl; benzoyl optionally substituted by amino, lower alkylamino or di-lower alkylamino; acetyl or cycloalkyl-carbonyl; and



signifies an aromatic 5-membered residue which is bonded via a N-atom and which contains further 1-3 N atoms in addition to the linking N atom,

15 as well as their pharmaceutically acceptable salts for the treatment or prevention of illnesses.

Some triazole derivatives which fall under formula I have been known for a long time. They are described e.g. in European Application No. 079 856 for use as active  
20 substances for agrochemical pest control, preferably for the control or prevention of an attack by microorganisms.

It has surprisingly been found that the compounds of general formula I are metabotropic glutamate receptor antagonists and/or agonists.

25

In the central nervous system (CNS) the transmission of stimuli takes place by the interaction of a neurotransmitter, which is sent out by a neuron, with a neuroreceptor.

L-Glutamic acid, the most commonly occurring neurotransmitter in the CNS, plays a critical role in a large number of physiological processes. The glutamate-dependent stimulus receptors are divided into two main groups. The first main group forms ligand-  
5 controlled ion channels. The metabotropic glutamate receptors (mGluR) belong to the second main group and, furthermore, belong to the family of G-protein-coupled receptors.

At present eight different members of these mGluR are known and of these some even have sub-types. On the basis of structural parameters, the different influences on the  
10 synthesis of secondary metabolites and the different affinity to low-molecular weight chemical compounds, these eight receptors can be sub-divided into three sub-groups:

mGluR1 and mGluR5 belong to group I, mGluR2 and mGluR3 belong to group II and mGluR4, mGluR6, mGluR7 and mGluR8 belong to group III.

15

The ligands of the metabotropic glutamate receptors belonging to the second group can be used for the treatment or prevention of acute and/or chronic neurological disorders such as restricted brain function caused by bypass operations or transplants, poor blood supply to the brain, spinal cord injuries, head injuries, hypoxia caused by pregnancy,  
20 cardiac arrest and hypoglycaemia.



Other treatable indications in this connection are Alzheimer's disease, Huntington's chorea, amyotrophic lateral sclerosis (ALS), dementia caused by AIDS, eye injuries, retinopathy, cognitive disorders, idiopathic parkinsonism or parkinsonism caused by  
25 medicaments as well as conditions which lead to glutamate-deficiency functions, such as e.g. muscle spasms, convulsions, migraine, urinary incontinence, nicotine addiction, psychoses, opiate addiction, anxiety, vomiting, chronic pain, dyskinesia, depressions and pains.

30

Objects of the present invention are the use of compounds of formula I and of their pharmaceutically acceptable salts as therapeutically active substances, as well as medicaments based on these compounds and their production, and novel compounds of

formula I and their pharmaceutically acceptable salts per se and as pharmaceutically active substances for the control or prevention of illnesses of the aforementioned kind.

Novel compounds of formula I are especially those in which R and R<sup>1</sup> have the

5 significance given above and  signifies an aromatic 5-membered ring which is bonded via a N atom and which contains further 1 or 3 N atoms in addition to the linking N atom or wherein R has the significance given above,  signifies an aromatic 5-membered ring which is bonded via a N atom and which contains a further 1-3 N atoms in addition to the linking N atom and R<sup>1</sup> signifies cycloalkyl.

10


The term "lower alkyl" used in the present description denotes straight-chain or branched saturated hydrocarbon residues with 1-7 carbon atoms, preferably with 1-4 carbon atoms, such as methyl, ethyl, n-propyl, i-propyl and the like.

15 The term "cycloalkyl" denotes cyclic saturated hydrocarbon residues with 3-7 carbon atoms in the ring, such as, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like.

The term "lower alkoxy" denotes lower alkyl residues in the sense of the foregoing  
20 definition which are bonded via an oxygen atom.

The term "halogen" embraces fluorine, chlorine, bromine and iodine.

In the scope of the present invention those compounds of general formula I in  
25 which R signifies chlorine, n is 1 or 2, R<sup>1</sup> signifies lower alkyl, cyclohexyl or benzyl and

 signifies an aromatic 5-membered ring which is bonded via a N atom and which contains further 2 or 3 N atoms in addition to the linking N atom are preferred for use as therapeutically active substances.

The following are examples of preferred compounds of general formula I:

1-[2-(2,4-dichloro-phenyl)-2-cyclohexyloxy-vinyl]-1H-[1,2,4]triazole,

1-[2-(2,4-dichloro-phenyl)-2-benzyloxy-vinyl]-1H-tetrazole,

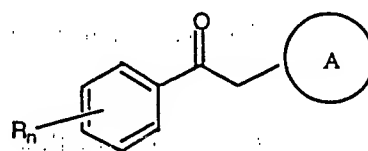
5 2-[2-(4-chloro-phenyl)-2-butoxy-vinyl]-2H-tetrazole,

1-[2-(4-chloro-phenyl)-2-butoxy-vinyl]-1H-[1,2,4]-triazole and


1-[2-(2,6-dichloro-phenyl)-2-butoxy-vinyl]-1H-[1,2,4]triazole.

The novel compounds of general formula I can be manufactured in accordance with the invention by alkylating or acylating a compound of the formula

10



II

wherein R, n and  have the significances given earlier,

and, if desired, converting a compound of formula I obtained into a pharmaceutically acceptable salt.

15

If desired, a functional group in a compound of formula I can be converted into a different functional group; in particular, amino groups can be alkylated to lower alkylamino or di-lower alkylamino groups or hydroxy groups can be alkylated. These

20

In the alkylation or acylation an acetophenone derivative of formula II is reacted with a suitable alkylating or acylating agent, preferably with benzyl bromide, benzoyl chloride, acetyl chloride, cyclohexyl triflate, cyclopropyl chloride, isopropyl bromide, n-butyl bromide, 4-methoxybenzyl chloride, isopropyl triflate, 4-dimethylaminobenzoyl chloride, benzyl chloride or the like. This reaction is effected according to known methods, preferably in the presence of sodium hydride. THF (tetrahydrofuran) and DMPU (1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone) in the ratio 3:1 is especially suitable as the solvent.

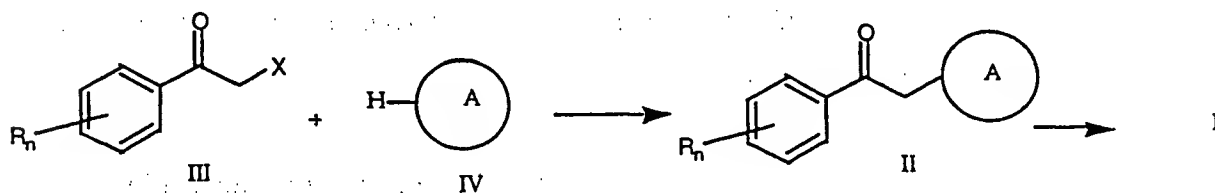
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This manufacturing variant is described in detail in Example I b).

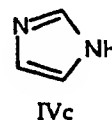
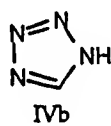
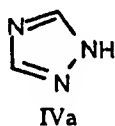
The pharmaceutically usable salts can be produced readily according to methods  
 5 known per se having regard to the nature of the compound to be converted into a salt.  
 Inorganic or organic acids such as, for example, hydrochloric acid, hydrobromic acid,  
 sulphuric acid, nitric acid, phosphoric acid or citric acid, formic acid, fumaric acid, maleic  
 acid, acetic acid, succinic acid, tartaric acid, methanesulphonic acid, p-toluenesulphonic  
 acid and the like are suitable for the formation of pharmaceutically usable salts of basic  
 10 compounds of formula I. Compounds which contain the alkali or alkaline earth metals, for  
 example sodium, potassium, calcium, magnesium or the like, basic amines or basic amino  
 acids are suitable for the formation of pharmaceutically usable salts of acidic compounds.

The following Scheme 1 illustrates the manufacture of the compounds of formula I  
 15 in overview, starting from the known compounds of formulae III and IV.

Scheme 1














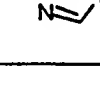
In this Scheme, R, n and  have the significances described above, X signifies  
 20 halogen, preferably chlorine or bromine. A compound of formula IV can preferably be a  
 triazole, tetrazole or imidazole of the general formulae

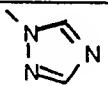
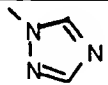
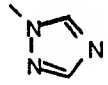
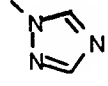

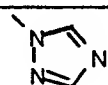
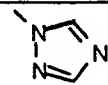
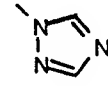
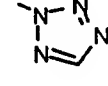
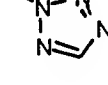
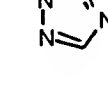
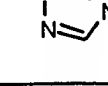
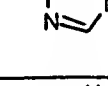
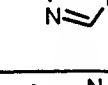
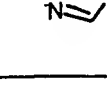





25 The compounds of general formulae II, III and IV are known or can be prepared  
 according to methods known per se.

The following Table 1 shows a selection of tested compounds for use as therapeutically active substances in a mGluR affinity test (see p. 9):

5

Compound No./ Example No.	R	R1	
A	2,4-Cl	i-Prop	
B	2,4-Cl	i-Bu	
C	2,4-Cl	n-Bu	
D	2,4,6-Cl	i-Prop	
E	2,4-Cl	CH <sub>3</sub>	
F	4-Br	n-Bu	
G	2,4-F	i-Prop	
H	4-F	i-Prop	
I	H	i-Prop	
J	4-Cl	n-Bu	
K	2,6-Cl	n-Bu	

L/1	2,4-Cl	Benzyl	
M/2	2,4-Cl	Benzoyl	
N/3	2,4-Cl	Acetyl	
O/4	2,4-Cl	Cyclohexyl	
P/5	2,4-Cl		
Q/6	4-CH <sub>3</sub>	i-Prop	
R/7	2,6-Cl	Benzyl	
S/8	2,4-Cl	n-Bu	
T/9	4-Cl	n-Bu	
U/10	2,6-Cl	i-Prop	
V/11	2,4-Cl	4-Methoxy-benzyl	
W/12	2,4-Cl	Benzoyl	
X/13	2,4-Cl	i-Prop	
Y/14	2,4-Cl	4-Dimethylamino-benzyl	

Z/15	2,4-Cl	Benzyl	
AA/16	2,4-Cl	i-Prop	
BB/17	2,4-Cl	n-Bu	

- A 1-[2-(2,4-Dichloro-phenyl)-2-isopropoxy-vinyl]-1H-[1,2,4]triazole
- B 1-[2-(2,4-Dichloro-phenyl)-2-isobutoxy-vinyl]-1H-[1,2,4]triazole
- C 1-[2-(2,4-Dichloro-phenyl)-2-butoxy-2-vinyl]-1H-[1,2,4]triazole
- 5 D 1-[2-(2,4,6-Trichloro-phenyl)-2-isopropoxy-vinyl]-1H-[1,2,4]triazole
- E 1-[2-(2,4-Dichloro-phenyl)-2-methoxy-vinyl]-1H-[1,2,4]triazole
- F 1-[2-(4-Bromo-phenyl)-2-butoxy-vinyl]-1H-[1,2,4]triazole
- G 1-[2-(2,4-Difluoro-phenyl)-2-isopropoxy-vinyl]-1H-[1,2,4]triazole
- H 1-[2-(4-Fluoro-phenyl)-2-isopropoxy-vinyl]-1H-[1,2,4]triazole
- 10 I 1-[2-(Phenyl)-2-isopropoxy-vinyl]-1H-[1,2,4]triazole
- J 1-[2-(4-Chloro-phenyl)-2-butoxy-vinyl]-1H-[1,2,4]triazole
- K 1-[2-(2,6-Dichloro-phenyl)-2-butoxy-vinyl]-1H-[1,2,4]triazole
- L 1-[2-(2,4-Dichloro-phenyl)-2-benzyloxy-vinyl]-1H-[1,2,4]triazole
- M 1-(2,4-Dichloro-phenyl)-2-[1,2,4]triazol-1-yl-vinyl-benzoic acid ester
- 15 N 1-(2,4-Dichloro-phenyl)-2-[1,2,4]triazol-1-yl-vinyl-acetic acid ester
- O 1-[2-(2,4-Dichloro-phenyl)-2-cyclohexyloxy-vinyl]-1H-[1,2,4]triazole
- P 1-(2,4-Dichloro-phenyl)-2-[1,2,4]triazol-1-yl-vinyl-cyclopropane  
carboxylic acid ester
- Q 1-[2-(4-Tolyl)-2-isopropoxy-vinyl]-1H-[1,2,4]triazole
- 20 R 1-[2-(2,6-Dichloro-phenyl)-2-benzyloxy-vinyl]-2H-tetrazole
- S 2-[2-(2,4-Dichloro-phenyl)-2-butoxy-vinyl]-2H-tetrazole
- T 2-[2-(4-Chloro-phenyl)-2-butoxy-vinyl]-2H-[1,2,4]tetrazole
- U 2-[2-(2,4-Dichloro-phenyl)-2-isopropoxy-vinyl]-2H-tetrazole
- V 2-[2-(2,4-Dichloro-phenyl)-2-(4-methoxy-benzyloxy)-vinyl]-2H-tetrazole
- 25 W 1-(2,4-Dichloro-phenyl)-2-tetrazol-1-yl-vinyl-benzoic acid ester
- X 1-[2-(2,4-Dichloro-phenyl)-2-isopropoxy-vinyl]-1H-tetrazole

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- Z 1-[2-(2,4-Dichloro-phenyl)-2-benzyloxy-vinyl]-1H-tetrazole
- AA 1-[2-(2,4-Dichloro-phenyl)-2-isopropoxy-vinyl]-1H-imidazole
- 5 BB 1-[2-(2,4-Dichloro-phenyl)-2-butoxy-vinyl]-1H-imidazole

As mentioned above, the compounds of formula I and their pharmaceutically acceptable salts are metabotropic glutamate receptor antagonists and/or agonists and can be used for the treatment or prevention of acute and/or chronic neurological disorders

10

The binding of the compounds of formula I in accordance with the invention to group II metabotropic glutamate receptors was determined in vitro. The preparations were tested in accordance with the test given hereinafter:

- 15 The GTP  $\gamma^{35}\text{S}$  test was used to determine the affinity of a compound to the group II mGluR. Membranes which adhere to the rat mGluR2 receptor were used. These were stimulated with 10  $\mu\text{M}$  1S,3R-ACPD.

- 20 The  $K_i$  values of the compounds to be tested are given. The  $K_i$  value is defined by the following formula

$$K_i = \frac{IC_{50}}{1 + \frac{[L]}{EC_{50}}}$$

- in which the  $IC_{50}$  values are those concentrations of the compounds to be tested in  $\mu\text{M}$  by which 50% of the effect of 1S,3R-ACPD are antagonized.  $[L]$  is the concentration of 1S,3R-ACPD and the  $EC_{50}$  value is the concentration of 1S,3R-ACPD in nM which brings about 50% stimulation.

Table 2

Activity on mGluR

Compound No./ Example No.	K <sub>i</sub> [μM] m-GluR2
A	1.17
B	0.64
C	1.40
D	2.70
E	11.00
F	0.66
G	7.60
H	10.00
I	12.70
J	0.60
K	0.60
L/1	0.43
M/2	1.20
N/3	4.70
O/4	0.10
P/5	2.40
Q/6	6.10
R/7	2.00
S/8	1.00
T/9	0.32
U/10	2.00
V/11	1.00
W/12	0.90
X/13	1.30
Y/14	1.40
Z/15	0.27
AA/16	7.71
BB/17	4.30

5

The compounds of formula I and pharmaceutically acceptable salts thereof can be used as medicaments, e.g. in the form of pharmaceutical preparations. The pharmaceutical preparations can be administered orally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions. However, the administration can also be effected rectally, e.g. in the form in suppositories, or parenterally, e.g. in the form of injections solutions.

10

The compounds of formula I and pharmaceutically acceptable salts thereof can be processed with pharmaceutically inert, inorganic or organic carriers for the production of pharmaceutical preparations. Lactose, corn starch or derivative thereof, talc, stearic acid or its salts and the like can be used, for example, as such carriers for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carriers for soft gelatine capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols and the like; depending on the nature of the active substance no carriers are, however, generally required in the case of soft gelatine capsules. Water, polyols, sucrose, invert sugar, glucose and the like are, for example, suitable carriers for the production of solutions and syrups. Adjuvants such as alcohols, polyols, glycerol, vegetable oils and the like can be used for aqueous injection solutions of water-soluble salts of compounds of formula I, but as a rule are not necessary. Suitable carriers for suppositories are, for example, natural or hardened oils, waxes, fats, semi-liquid or liquid polyols and the like.

Moreover, the pharmaceutical preparations can contain preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents or antioxidants. They can also contain still other therapeutically valuable substances.

As mentioned earlier, medicaments containing a compound of formula I or a pharmaceutically acceptable salt thereof and a therapeutically inert excipient are also an object of the present invention, furthermore also a process for the production of such medicaments, which is characterized by bringing one or more compounds of formula I or pharmaceutically acceptable salts thereof and, if desired, one or more other therapeutically valuable substances into a galenical dosage form together with one or more therapeutically inert carriers.

The dosage can vary within wide limits and will, of course, be fitted to the individual requirements in each particular case. In general, the effective dosage for oral or parenteral administration is between 0.01-20 mg/kg/day, with a dosage of 0.1-10 mg/kg/day being preferred for all of the indications described. The daily dosage for an adult human being of 70 kg body weight accordingly lies between 0.7-1400 mg per day, preferably between 7 and 700 mg per day.

The following Examples are intended to illustrate the manufacture of the specific novel compounds in more detail.

5

Example 11-[2-2-(2,4-Dichloro-phenyl)-vinyl]-2-benzyloxy-1H-[1,2,4]triazole

- a) 10 g (44.8 mmol) of 2,2',4'-trichloroacetophenone were added portionwise at room  
10 temperature to a solution of 9.3 g (134 mmol) of triazole in 50 ml of dimethylformamide  
and stirred at 80°C for 16 hours. The reaction mixture was added to 100 ml of 2N sodium  
hydroxide solution and extracted three times with 100 ml of ethyl acetate each time. The  
combined organic phases were dried over magnesium sulphate and concentrated in a  
vacuum. The crude product was purified by column chromatography on silica gel (ethyl  
15 acetate/methanol 100:5). 2.8 g (25%) of 1-(2,4-dichlorophenyl)-2-[1,2,4]triazol-1-yl-  
ethanone were obtained as a yellow-brown solid.
- b) 670 mg (2.62 mmol) of 1-(2,4-dichlorophenyl)-2-[1,2,4]triazol-1-yl-ethanone in  
12 ml of tetrahydrofuran and 4 ml of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone  
20 were added to a suspension of 171 mg (3.92 mmol) of sodium hydride (55% in mineral oil)  
in 15 ml of tetrahydrofuran and 5 ml of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimi-  
dinone (DMPU) and stirred at room temperature for 3 hours. Thereafter, 396 mg  
(5.24 mmol) of benzyl bromide were added and [the mixture] was stirred at room temper-  
ature for a further 16 hours. The tetrahydrofuran was removed under a vacuum, the residue  
25 was added to 50 ml of water and extracted three times with 50 ml of diethyl ether each  
time. The combined organic phases were dried over magnesium sulphate and the diethyl  
ether was removed in a vacuum. The crude product was purified by column chroma-  
tography on silica gel (diethyl ether/pentane 1:4). In addition to mixed fractions with the  
C-alkylation product there were obtained 65 mg (7%) of pure 1-[2-(2,4-dichloro-phenyl)-2-  
30 benzyloxy-vinyl]-1H-[1,2,4]triazole as a colourless oil.  $[M+H]^+ = 345, 347$ .

Example 21-(2,4-Dichloro-phenyl)-2-[1,2,4]triazole-1-vinyl-benzoic acid ester

5           Analogously to Example 1a,b, after reacting 1-(2,4-dichlorophenyl)-2-[1,2,4]-triazol-1-yl-ethanone with benzoyl chloride there was obtained pure 1-(2,4-dichloro-phenyl)-2-[1,2,4]triazole-1-vinyl-benzoic acid ester. After reaction with oxalic acid there was obtained a salt of the composition  $C_{17}H_{11}N_3O_2Cl_2 \cdot 2 C_2H_2O_4$  with a melting point of 130°C.

10

Example 31-(2,4-Dichloro-phenyl)-2-[1,2,4]triazol-1-yl-vinyl-acetic acid ester

15           Analogously to Example 1a,b, after reacting 1-(2,4-dichlorophenyl)-2-[1,2,4]-triazol-1-yl-ethanone with acetyl chloride there was obtained 1-(2,4-dichloro-phenyl)-2-[1,2,4]triazol-1-yl-vinyl-acetic acid ester as a white solid with m.p. 127°C.

Example 4

20

1-[2-(2,4-Dichloro-phenyl)-2-cyclohexyloxy-vinyl]-1H-[1,2,4]triazole

          Analogously to Example 1a,b, after reacting 1-(2,4-dichlorophenyl)-2-[1,2,4]-triazol-1-yl-ethanone with cyclohexyl triflate there was obtained 1-[2-(2,4-dichloro-phenyl)-1-cyclohexyloxy-vinyl]-1H-[1,2,4]triazole as a white solid with m.p. 84°C.

25

Example 51-(2,4-Dichloro-phenyl)-2-[1,2,4]triazol-1-yl-vinyl-cyclopropanecarboxylic acid ester

30

          Analogously to Example 1a,b, after reacting 1-(2,4-dichlorophenyl)-2-[1,2,4]-triazol-1-yl-ethanone with cyclopropoyl chloride there was obtained 1-(2,4-dichloro-

phenyl)-2-[1,2,4]triazol-1-yl-vinyl-cyclopropanecarboxylic acid ester as a white solid with m.p 108°C.

#### Example 6

5

#### 1-[2-(4-Tolyl)-2-isopropoxy-vinyl]-1H-[1,2,4]triazole

Analogously to Example 1a,b, after reacting 1-(4-methylphenyl)-2-[1,2,4]triazol-1-yl-ethanone with isopropyl bromide there was obtained 1-[2-(4-tolyl)-2-isopropoxy-vinyl]-  
10 1H-[1,2,4]triazole. After reaction with HCl in dioxan there was obtained a salt of the composition  $C_{14}H_{17}N_3O \cdot HCl$ .  $[M+H]^+ = 243$ .

#### Example 7

#### 15 1-[2-(2,6-Dichloro-phenyl)-2-benzyloxy-vinyl]-1H-[1,2,4]triazole

Analogously to Example 1a,b, after reacting 1-(2,6-dichlorophenyl)-2-[1,2,4]-triazol-1-yl-ethanone with benzyl chloride there was obtained 1-[2-(2,6-dichloro-phenyl)-2-benzyloxy-vinyl]-1H-[1,2,4]triazole. After reaction with oxalic acid there was obtained a  
20 salt with the composition  $C_{17}H_{13}N_3OCl_2 \cdot C_2H_2O_4$ , which decomposed at  $> 71^\circ C$ .

#### Example 8

#### 25 2-[2-(2,4-Dichloro-phenyl)-2-butoxy-vinyl]-2H-[1,2,4]tetrazole

25

a) A solution of 15.9 g (71 mmol) of 2,2',4'-trichloroacetophenone in 100 ml of methylene chloride was slowly added dropwise while cooling with ice to a solution of 4.98 g (71 mmol) of tetrazole and 14.4 g (142 mmol) of triethylamine in 100 ml of methylene chloride and heated under reflux for 16 hours. The reaction mixture was added  
30 to 100 ml of water and extracted three times with 100 ml of methylene chloride each time. The combined organic phases were dried over magnesium sulphate and concentrated in a vacuum. The crude product was purified by column chromatography on silica gel (ethyl

acetate/hexane 1:1). There were obtained 4.75 g (26%) of 1-(2,4-dichloro)-2-tetrazol-1-yl-ethanone and 7.80 g (43%) of 1-(2,4-dichlorophenyl)-2-tetrazol-2-yl-ethanone.

- b) Analogously to Example 1b, after reacting 1-(2,4-dichlorophenyl)-2-tetrazol-2-yl-ethanone with n-butyl bromide there was obtained 2-[2-(2,4-dichloro-phenyl)-2-butoxy-vinyl]-2H-[1,2,4]tetrazole as a colourless oil.  $[M+H]^+ = 313$ .

#### Example 9

##### 10 2-[2-(4-Chloro-phenyl)-2-butoxy-vinyl]-2H-[1,2,4]tetrazole

Analogously to Example 7a,b, after reacting 1-(4-chlorophenyl)-2-tetrazol-2-yl-ethanone with n-butyl bromide there was obtained 2-[2-(4-chloro-phenyl)-2-butoxy-vinyl]-2H-tetrazole as a colourless oil.  $[M+H]^+ = 279$ .

15

#### Example 10

##### 2-[2-(2,4-Dichloro-phenyl)-2-isopropoxy-vinyl]-2H-tetrazole

- 20 Analogously to Example 7a,b, after reacting 1-(2,4-dichlorophenyl)-2-tetrazol-2-yl-ethanone with isopropyl bromide there was obtained 2-[2-(2,4-dichloro-phenyl)-2-isopropoxy-vinyl]-2H-tetrazole as a colourless oil.  $[M]^+ = 299$ .

#### Example 11

25

##### 2-[2-(2,4-Dichloro-phenyl)-2-(4-methoxy-benzyloxy)-vinyl]-2H-tetrazole

- Analogously to Example 7a,b, after reacting 1-(2,4-dichlorophenyl)-2-tetrazol-2-yl-ethanone with 4-methoxybenzyl chloride there was obtained 2-[2-(2,4-dichloro-phenyl)-2-(4-methoxy-benzyloxy)-vinyl]-2H-tetrazole as a colourless oil.  $[M+H]^+ = 376$ .

30

Example 121-(2,4-Dichloro-phenyl)-2-tetrazol-1-yl-vinyl-benzoic acid ester

5 Analogously to Example 7a,b, after reacting 1-(2,4-dichlorophenyl)-2-tetrazol-1-yl-ethanone with benzoyl chloride there was obtained 1-(2,4-dichloro-phenyl)-2-tetrazol-1-yl-vinyl-benzoic acid ester as a colourless oil.  $[M]^+ = 360$ .

Example 13

10

1-[2-(2,4-Dichloro-phenyl)-2-isopropoxy-vinyl]-1H-tetrazole

Analogously to Example 7a,b, after reacting 1-(2,4-dichlorophenyl)-2-tetrazol-1-yl-ethanone with isopropyl triflate there was obtained 1-[2-(2,4-dichloro-phenyl)-2-isopro-

15 poxy-vinyl]-1H-tetrazole as a white powder with m.p. 82°C.

Example 14

20

1-(2,4-Dichloro-phenyl)-2-tetrazol-1-yl-vinyl-4-dimethylamino-benzoic acid ester

Analogously to Example 7a,b, after reacting 1-(2,4-dichlorophenyl)-2-tetrazol-1-yl-ethanone with 4-dimethylamino-benzoyl chloride there was obtained 1-(2,4-dichloro-phenyl)-2-tetrazol-1-yl-vinyl-4-dimethylamino-benzoic acid ester as colourless crystals with m.p. 135°C.

25

Example 151-[2-(2,4-Dichloro-phenyl)-2-benzyloxy-vinyl]-1H-tetrazole

30

Analogously to Example 7a,b, after reacting 1-(2,4-dichlorophenyl)-2-tetrazol-1-yl-ethanone with benzyl chloride there was obtained 1-[2-(2,4-dichloro-phenyl)-2-benzyloxy-vinyl]-1H-tetrazole as colourless crystals with m.p. 92°C.

Example 161-[2-(2,4-Dichloro-phenyl)-2-isopropoxy-vinyl]-1H-imidazole

5

a) Analogously to Example 1a, after reacting 2,2',4'-trichloroacetophenone with imidazole there was obtained 1-(2,4-dichlorophenyl)-2-(1H-imidazol)-1-yl-ethanone.

b) Analogously to Example 1b, after reacting 1-(2,4-dichlorophenyl)-2-(1H-imidazol)-  
10 1-yl-ethanone with isopropyl bromide there was obtained 1-[2-(2,4-dichloro-phenyl)-2-isopropoxy-vinyl]-1H-imidazole, which was isolated as a salt of the composition  $C_{14}H_{14}Cl_2N_2O \cdot HCl$  with m.p. 184-186°C.

Example 17

15

1-[2-(2,4-Dichloro-phenyl)-2-butoxy-vinyl]-1H-imidazole

Analogously to Example 16a,b, after reacting 1-(2,4-dichlorophenyl)-2-(1H-imidazol)-1-yl-ethanone with n-butyl bromide there was obtained 1-[2-(2,4-dichloro-  
20 phenyl)-2-butoxy-vinyl]-1H-imidazole, which was isolated as salt of the composition  $C_{15}H_{16}Cl_2N_2O \cdot HCl$  with m.p. 205-207°C.

Example A

Tablets of the following compositions are produced in the usual manner:

5		<u>mg/tablet</u>
	Active ingredient	100
	Powd. lactose	95
	White corn starch	35
	Polyvinylpyrrolidone	8
10	Na carboxymethylstarch	10
	Magnesium stearate	2
	Tablet weight	250

Example B

15

Tablets of the following composition are produced in a conventional manner:

		<u>mg/tablet</u>
	Active ingredient	200
20	Powd. lactose	100
	White corn starch	64
	Polyvinylpyrrolidone	12
	Na carboxymethylstarch	20
	Magnesium stearate	4
25	Tablet weight	400

Example C

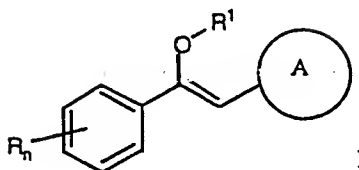
Capsules of the following composition are produced:

5		<u>mg/capsule</u>
	Active ingredient	50
	Cryst. lactose	60
	Microcrystalline cellulose	34
	Talc	5
10	Magnesium stearate	<u>1</u>
	Capsule fill weight 150	

The active ingredient having a suitable particle size, the crystalline lactose and the microcrystalline cellulose are homogeneously mixed with one another, sieved and thereafter talc and magnesium stearate are admixed. The finished mixture is filled into  
15 hard gelatine capsules of suitable size.

Claims

## 1. Use of compounds of the general formula



5

wherein

R signifies halogen or lower alkyl;

n signifies 0-3;

- 10 R<sup>1</sup> signifies lower alkyl; cycloalkyl; benzyl optionally substituted by hydroxy, halogen, lower alkoxy or lower alkyl; benzoyl optionally substituted by amino, lower alkyl-amino or di-lower alkylamino; acetyl or cycloalkyl-carbonyl; and



- signifies an aromatic 5-membered residue which is bonded via a N-atom and which contains further 1-3 N atoms in addition to the linking N atom,  
 15 as well as their pharmaceutically acceptable salts as therapeutically active substances.

20

2. Use of compounds of general formula I in accordance with claim 1 for the control or prevention of acute and/or chronic neurological disorders and, respectively, for the production of corresponding medicaments.

3. Use of compounds of general formula I in accordance with claims 1 and 2, wherein

R signifies chlorine,

- 25 n signifies 1 or 2,

R<sup>1</sup> signifies lower alkyl, cyclohexyl or benzyl and


signifies an aromatic 5-membered ring which is bonded via a N atom and which contains further 2 or 3 N atoms in addition to the linking N atom.


## 4. Use of

- 1-[2-(2,4-dichloro-phenyl)-2-cyclohexyloxy-vinyl]-1H-[1,2,4]triazole,  
 5 1-[2-(2,4-dichloro-phenyl)-2-benzyloxy-vinyl]-1H-tetrazole,  
 2-[2-(4-chloro-phenyl)-2-butoxy-vinyl]-2H-tetrazole,  
 1-[2-(4-chloro-phenyl)-2-butoxy-vinyl]-1H-[1,2,4]triazole and  
 1-[2-(2,6-dichloro-phenyl)-2-butoxy-vinyl]-1H-[1,2,4]triazole

in accordance with claim 3.

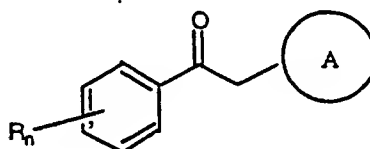
10

5. Compounds of general formula I, wherein R and R<sup>1</sup> have the significances given  
 in claim 1 and  signifies an aromatic 5-membered ring which is bonded via a N atom  
 and which contains further 1 or 3 N atoms in addition to the linking N atom.


6. Compounds of general formula I, wherein R and  have the significances  
 15 set forth in claim 1 and R<sup>1</sup> signifies cycloalkyl.

7. 1-[2-(2,4-Dichloro-phenyl)-2-cyclohexyloxy-vinyl]-1H-[1,2,4]triazole in  
 accordance with claim 6.

- 20 8. A process for the manufacture of compounds in accordance with claims 5-7,  
 which process comprises alkylating or acylating a compound of the formula



II

- wherein R, n and  have the significances given in claim 1,  
 25 and, if desired, converting a compound of formula I obtained into a pharmaceutically  
 acceptable salt.

9. Compounds in accordance with claims 5-7 for use as therapeutically active substances.

5           10. Use of compound in accordance with claims 5-7 in the control or prevention of illnesses, especially for the control or prevention of acute and/or chronic neurological disorders and, respectively, for the production of corresponding medicaments.

          11. A medicament containing one or more compounds of general formula I and a  
10   therapeutically inert excipient.

          12. A medicament in accordance with claim 11 for the control or prevention of illnesses, especially for the control or prevention of acute and/or chronic neurological disorders.

15

13 The invention as herein described.

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# INTERNATIONAL SEARCH REPORT

International Application No.

PCT/EP 98/04890

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K31/41 C07D257/04 C07D233/60 C07D249/08

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 34 17 468 A (BAYER AG) 14 November 1985 * see in particular claims 1,5,7,9; p. 22; 1.20-p.23, 1.14 *	1,5,8-12
X	DE 28 39 388 A (SIEGFRIED AG) 27 March 1980 * see in particular examples 8,9 and claim 2;	1,5,8-12
X	ZIRNGIBL : "Structure-activity relationships of 2-(1H-Imidazol-1-yl)vinyl ethers" ANN. N.Y.ACAD. SCI., vol. 544, 1988, pages 63-73, XP002086514 *see in particular Figure 6 & Tables 5-7*	1,5,8-12

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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

\* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

3 December 1998

Date of mailing of the international search report

22.01.99

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# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP 98/04890

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 82 02552 A (SIEGFRIED AG ;ZIRNGIBL LUDWIG (CH); THIELE KURT (CH)) 5 August 1982 *see examples 1,6* ---	5
X	CHEMICAL ABSTRACTS, vol. 97, no. 19, 8 November 1982 Columbus, Ohio, US; abstract no. 162901z, page 710; XP002086516 see abstract & ANON: "Imidazole and triazole derivatives" RES. DISCL., vol. 218, 1982, page 233 ----	5
A	SCHAFFHAUSER ET AL.: "Pharmacological characterization of metabotropic glutamate receptors linked to the inhibition of adenylate cyclase activity in rat striatal slices" NEUROPHARMACOLOGY, vol. 36, no. 7, July 1997, pages 933-940, XP002086515 *see in particular summary, and Fig. 1 (p.935) * -----	1-12
A	EP 0 079 856 A (CIBA GEIGY AG) 25 May 1983 cited in the application * see Table 1; claims 1-6; p.11, 1.14- p.12, 1.8 * -----	1-12

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/EP 98/04890

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely
  
2. ☒ Claims Nos.: 13  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
Claim 13 does not contain a particular technical feature
  
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
  
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
  
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
  
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 98/04890

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 3417468 A	14-11-1985	AU 4223685 A	14-11-1985
		BR 8502226 A	14-01-1986
		DD 235173 A	30-04-1986
		DK 207585 A	12-11-1985
		EP 0160931 A	13-11-1985
		GR 851124 A	25-11-1985
		JP 60260560 A	23-12-1985
		US 4764526 A	16-08-1988
DE 2839388 A	27-03-1980	AR 227379 A	29-10-1982
		AT 5319 T	15-12-1983
		AU 529481 B	09-06-1983
		AU 5073179 A	20-03-1980
		CA 1128053 A	20-07-1982
		DK 376379 A,B,	12-03-1980
		EP 0008804 A	19-03-1980
		FI 792783 A,B,	12-03-1980
		GR 73091 A	01-02-1984
		HR 970093 B	30-04-1997
		IE 48820 B	29-05-1985
		JP 1325887 C	16-07-1986
		JP 55038394 A	17-03-1980
		JP 60052147 B	18-11-1985
		US 4330545 A	18-05-1982
		US 4210657 A	01-07-1980
		ZA 7904743 A	24-09-1980
WO 8202552 A	05-08-1982	CH 648552 A	29-03-1985
		AT 9796 T	15-10-1984
		EP 0069754 A	19-01-1983
		JP 57502215 T	16-12-1982
		US 4554356 A	19-11-1985
EP 0079856 A	25-05-1983	AU 9036282 A	19-05-1983
		BR 8206569 A	27-09-1983
		DK 502582 A	13-05-1983
		GR 78403 A	27-09-1984
		JP 58090565 A	30-05-1983
		PT 75830 B	21-01-1986
		ZA 8208267 A	28-09-1983